(4) a sequence that is degenerate as a result of the genetic code with respect to a sequence defined in (1), (2) or (3); or

(b) is a sequence complementary to a polynucleotide defined in (a).

47. (New) An isolated polynucleotide according to claim 46 which is a DNA sequence.

48. (New) An isolated polynucleotide which encodes an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 4, 6, 8, 19 and 12.

49. (New) An isolated polypeptide which has methylarginase activity and which comprises a sequence selected from the group consisting of SEQ ID NO: 2, 4, 6, 8, 10 and 12, a sequence substantially homologous thereto or a fragment of either said sequence.

50. (New) A vector incorporating a polynucleotide which

(a) encodes a polypeptide that has the properties of a methylarginase, which polynucleotide is selected from the group consisting of:

(1) the coding sequence of SEQ ID NO: 1, 3, 5, 7, 9 or 11;

(2) a fragment of a sequence defined in (1);

(3) a sequence which hybridises selectively to the complement of a sequence defined in (1) or (2); and

(4) a sequence that is degenerate as a result of the genetic code with respect to a sequence defined in (1), (2) or (3); or

(b) is a sequence complementary to a polynucleotide defined in (a).

51. (New) A vector according to claim 50, which is an expression vector.

52. (New) A cell harbouring

a polynucleotide which:

(a) encodes a polypeptide that has the properties of a methylarginase, which polynucleotide is selected from the group consisting of:

(1) the coding sequence of SEQ ID NO: 1, 3, 5, 7, 9 or 11;

(2) a fragment of a sequence defined in (1);

(3) a sequence which hybridises selectively to the complement of a sequence defined in (1) or (2); and

(4) a sequence that is degenerate as a result of the genetic code with respect to a sequence defined in (1), (2) or (3); or

(b) is a sequence complementary to a polynucleotide defined in (a),

a polypeptide which has methylarginase activity and which comprises a sequence selected from the group consisting of SEQ ID NO: 2, 4, 6, 8, 10 and 12, a sequence substantially homologous thereto or a fragment of either said sequence or

a vector incorporating a said polynucleotide.

53. (New) A process for the preparation of a polypeptide which has methylarginase activity, which process comprises the steps of cultivating a host cell harbouring an expression vector according to claim 51 under conditions to provide for expression of the said polypeptide, and recovering the expressed polypeptide.

54. (New) An antibody capable of binding

a polypeptide encoded by a polynucleotide which:

(a) encodes a polypeptide that has the properties of a methylarginase, which polynucleotide is selected from the group consisting of:

(1) the coding sequence of SEQ ID NO: 1, 3, 5, 7, 9 or 11;

(2) a fragment of a sequence defined in (1);

(3) a sequence which hybridises selectively to the complement of a sequence defined in (1) or (2); and

(4) a sequence that is degenerate as a result of the genetic code with respect to a sequence defined in (1), (2) or (3); or

(b) is a sequence complementary to a polynucleotide defined in (a) or

a polypeptide which has methylarginase activity and which comprises a sequence selected from the group consisting of SEQ ID NO: 2, 4, 6, 8, 10 and 12, a sequence substantially homologous thereto or a fragment of either said sequence.

55. (New) A non-human animal which is not capable of expressing or is not capable of expressing an active form of one or more isoforms of methylarginase.

56. (New) A non-human animal according to claim 55, wherein the methylarginase isoform is a dimethylarginine dimethylaminohydrolase I (DDAHI) or dimethylaminohydrolase II (DDAHI).

57. (New) A non-human animal according to claim 55 which is a transgenic animal.

58. (New) A non-human animal according to claim 57 which is a mouse.

59. (New) A modulator of methylarginase activity and/or expression.

60. (New) A modulator according to claim 59, which is an inhibitor of methylarginase activity and/or expression.

61. (New) A modulator according to claim 59, which is an activator of methylarginase activity and/or expression.

62. (New) A modulator according to claim 60, which is an inhibitor of a bacterial methylarginase.

63. (New) A modulator according to claim 59, wherein the methylarginase is a DDAHI or DDAII II.

64. (New) A method for identifying a modulator of methylarginase activity and/or expression, the method comprising the steps of:

(i) contacting a test substance and

a polynucleotide which:

(a) encodes a polypeptide that has the properties of a methylarginase, which polynucleotide is selected from the group consisting of:

(1) the coding sequence of SEQ ID NO: 1, 3, 5, 7, 9 or 11;

(2) a fragment of a sequence defined in (1);

(3) a sequence which hybridises selectively to the complement of a sequence defined in (1) or (2); and

(4) a sequence that is degenerate as a result of the genetic code with respect to a sequence defined in (1), (2) or (3); or

(b) is a sequence complementary to a polynucleotide defined in (a),

a polypeptide which has methylarginase activity and which comprises a sequence selected from the group consisting of SEQ ID NO: 2, 4, 6, 8, 10 and 12, a sequence substantially homologous thereto or a fragment of either said sequence,

a vector incorporating a said polynucleotide or

a cell harbouring a said polynucleotide, polypeptide or vector

under conditions that would permit methylarginase activity in the absence of the test substance; and

(ii) determining thereby whether the said substance modulates the activity and/or expression of methylarginase.

65. (New) A method according to claim 64 further comprising the step of formulating a modulator identified in step (ii) with a pharmaceutically acceptable carrier or diluent.

66. (New) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and/or diluent and

a polynucleotide which:

(a) encodes a polypeptide that has the properties of a methylarginase, which polynucleotide is selected from the group consisting of:

(1) the coding sequence of SEQ ID NO: 1, 3, 5, 7, 9 or 11;

(2) a fragment of a sequence defined in (1);

(3) a sequence which hybridises selectively to the complement of a sequence defined in (1) or (2); and

(4) a sequence that is degenerate as a result of the genetic code with respect to a sequence defined in (1), (2) or (3); or

(b) is a sequence complementary to a polynucleotide defined in (a),

a polypeptide which has methylarginase activity and which comprises a sequence selected from the group consisting of SEQ ID NO: 2, 4, 6, 8, 10 and 12, a sequence substantially homologous thereto or a fragment of either said sequence,

an expression vector incorporating a said polynucleotide or

a modulator of methylarginase activity and/or expression.

67. (New) A method of treating a human or animal suffering from a condition selected from the group consisting of hyperlipidaemia, renal failure, hypertension, restenosis after angioplasty, atherosclerosis, complications of heart failure, schizophrenia, multiple sclerosis and cancer, which method comprises the step of administering to the host a therapeutically effective amount of

a polypeptide which has methylarginase activity and which comprises a sequence selected from the group consisting of SEQ ID NO: 2, 4, 6, 8, 10 and 12, a sequence substantially homologous thereto or a fragment of either said sequence,

an expression vector incorporating a polynucleotide which:

(a) encodes a polypeptide that has the properties of a methlarginase, which polynucleotide is selected from the group consisting of:

(1) the coding sequence of SEQ ID NO: 1, 3, 5, 7, 9 or 11;

(2) a fragment of a sequence defined in (1);

(3) a sequence which hybridises selectively to the complement of a sequence defined in (1) or (2); and

(4) a sequence that is degenerate as a result of the genetic code with respect to a sequence defined in (1), (2) or (3); or

(b) is a sequence complementary to a polynucleotide defined in (a), or

a modulator which is an inhibitor of methylarginase activity and/or expression.

68. (New) A method of treating a human or animal suffering from a condition selected from the group consisting of ischeamia-reperfusion injury of the brain or heart, cancer, lethal hypotension in severe inflammatory conditions such as septic shock or multi-organ failure, or local and systemic inflammatory disorders including arthritis, skin disorders, inflammatory cardiac disease, migraine and a bacterial infection, which method comprises the step of administering to the host a therapeutically effective amount of a modulator which is an inhibitor of methylarginase activity and/or expression.

69. (New) A method according to claim 68, which further comprises administering to the host a methylarginine.

70. (New) A method according to claim 69, wherein the methylarginine is L-NMMA.

REMARKS

The above amendments are made to place the claims in a more traditional format.

Respectfully submitted,

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